



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of
MEISEL et al.

Appln. No.: 09/181,671

Group Art Unit: 1621

Filed: October 29, 1998

Examiner: B. Davis

For: NOVEL MODIFICATIONS OF 2-AMINO...

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DECLARATION OF WILFRIED THIEL

Hon. Commission of Patents
And Trademarks
Washington, D.C. 20231

Sir.

I, Wilfried Thiel, declare and state as follows:

1. I studied chemistry at the Technical University of Dresden (from 1971 to 1975) and graduated 1975 as qualified chemist. After research studies in Organic Chemistry at the Technical University of Dresden (from 1975 to 1978), I received the Doctor of Science degree in 1978.

Thereafter, I was employed as assistant in a research laboratory of the chemical factory VEB Chemiekombinat Bitterfeld/Farbenfabrik Wolfen at the Technical University of Dresden. I worked in applied research, in particular in the field of synthesis and analytics of dyes and chemical intermediates, but also in basic research in the field of haloacetic acid derivatives and sulfur chemistry.

In 1988, I was awarded the qualification as university lecturer. The title of my postdoctoral thesis is: "Chloroacetic acid derivatives as building blocks for thiooxalic acid derivatives and heterocycles".

Since 1988, I have headed the Department of Analytics of Active Substances of the Arzneimittelwerk Dresden GmbH.

Since 1976, I have authored about 34 publications and 80 patent documents as well as several Drug Master Files for active pharmaceutical ingredients.

2. Patent background information

The compound 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino-benzene (Retigabine) and its preparation is described in patent DE 42 00 259. This compound has, for example, anticonvulsant, antipyretic and analgesic activity and thus can be used in pharmaceutical preparations. By crystallizing the compounds, different products in respect to crystal size and form have been obtained, but there was no indication of the existence of crystalline modifications (polymorphs) prior to our discovery. Mixtures of crystalline modifications are a great problem for pharmaceutical preparations.

3. The Invention

My co-inventors and I determined that the compound 2-amino-4-(4-fluorobenzylamino)-1ethoxycarbonyl-amino-benzene can exist as crystalline modifications (polymorphs). Each of our three discovered modifications can be prepared in pure homogeneous form. The three modifications, named A, B and C, have different physicochemical properties. Each modification has a characteristic X-ray powder diffractogram.

4. As an example, the X-ray powder diffractograms of two typical batches, which were manufactured in 1994, before the discovery of polymorphism, are compared with the pure crystalline modifications A, B and C as overlay. Batches 9403002 and 9404001 were manufactured in pilot plant scale and exist as mixtures of crystalline modifications (see attached figures 1 and 2).

The black curves in Figure 1 and 2 represent diffractograms of the prior art batches of Retigabine. The diffractograms of batch 9403002 and 9404001 are different. As a result of our discovery of the three modifications, the reflexes in diffractograms of the prior art batches can be assigned to the modifications, the reflexes in diffractograms of the prior art batches can be assigned to the modifications A, B, C, which were unknown previously.

Figure 1:

In addition to the characteristic pattern of modification C (green curve) the powder diffractogram of sample 9403002 (black curve) shows an additional peak at 20.0° 2-Theta which can be assigned to the strongest peak of modification A. The crystallize of this sample consists of modification C, with a small amount of modification A.

Figure 2:

The comparison of the powder diffractogram of sample 9404001 (black curve) with those of the pure modification A and B (red and blue curve) shows that this crystallize represents a mixture of modification A and B. Modification A is the main product in this mixture. The presence of modification B is indicated by the weak peak at 5.0° 2-Theta which occurs as the strongest peak in the characteristic pattern of this polymorph.

5. Summary

It has been proven that the compound 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonyl-amino-benzene can exist as crystalline modifications (polymorphs). Each of our three discovered modifications can be prepared in pure homogeneous form. The three modifications, called A, B and C, have different physicochemical properties. Each modification has a characteristic X-ray powder diffractogram.

6. I declare further that all statements made on information and belief are believed true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Patent and Trademark Office's Code. I understand that such willfully false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

By: Wilfried Thiel Date: June 23, 2005

Batch 9403002 (manufacturing date:March 31, 1994) - prior art

modification A
modification B
modification C

claimed in

our patent application

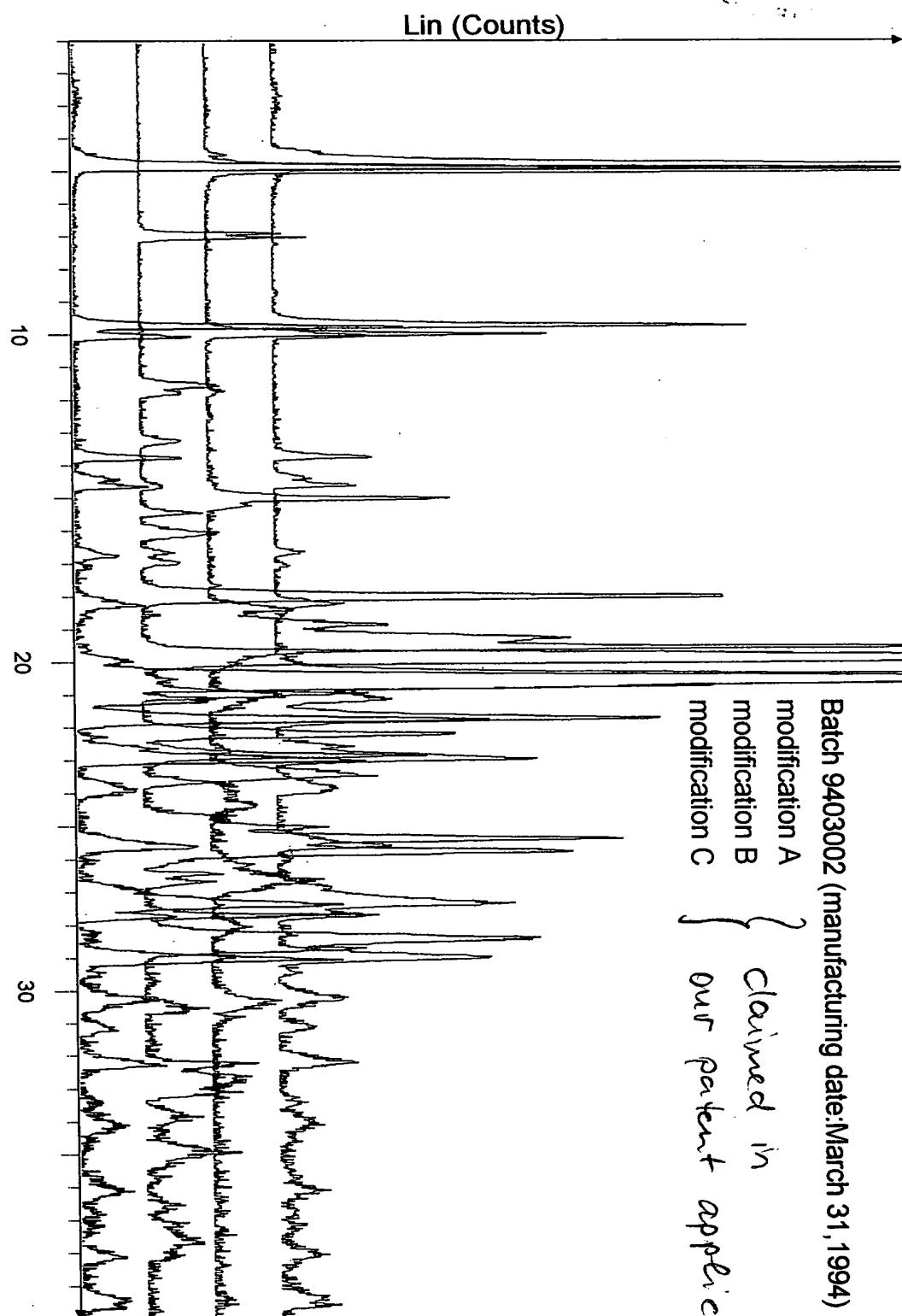


Figure 1:

2-Theta - Scale

Batch 9404001 (manufacturing date: April 13, 1994) - prior art

modification A }
modification B } claimed in
modification C } our patent application

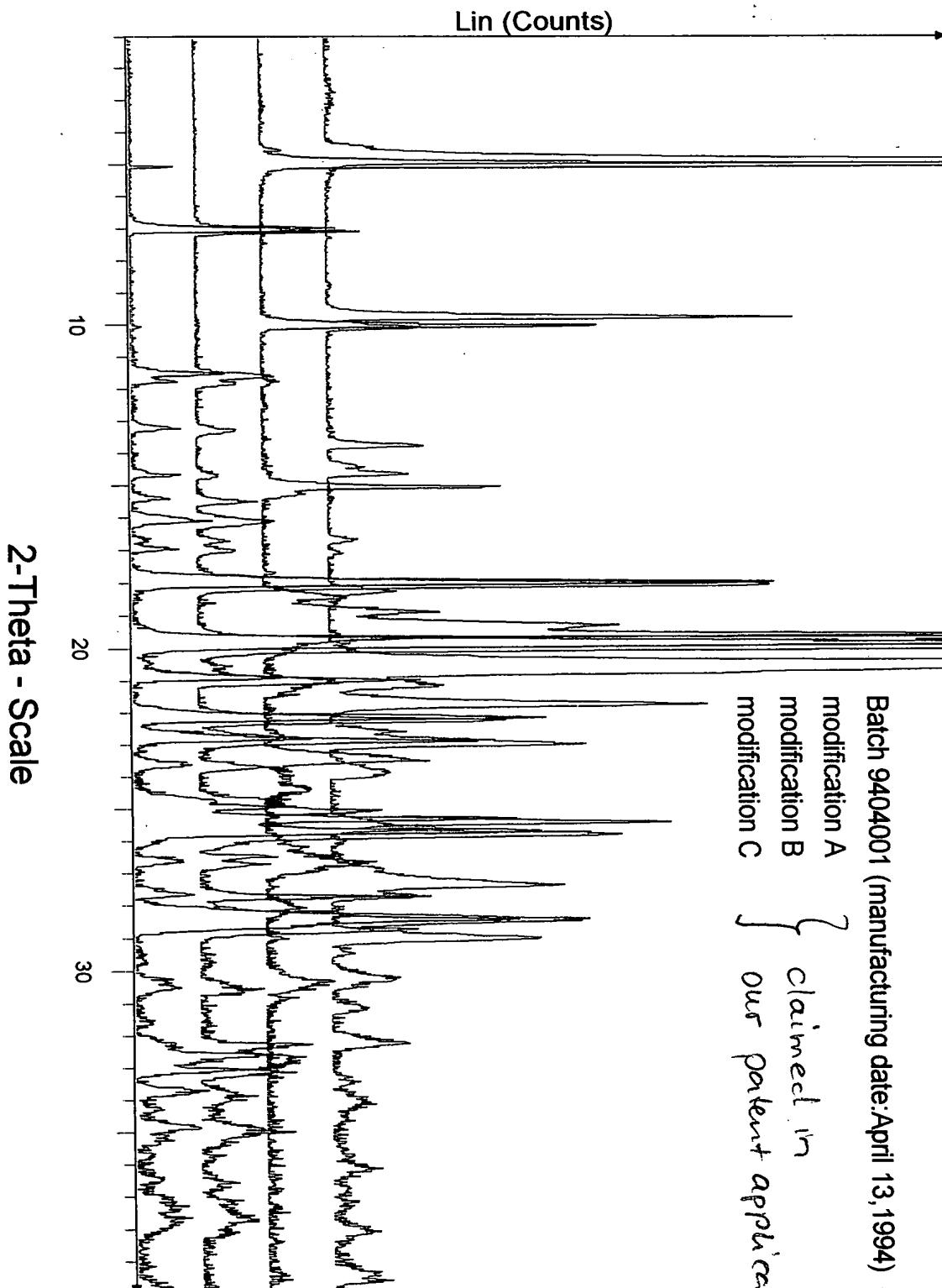


Figure 2: